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expression may be monitored using nucleic acid probes to the DNA or RNA equivalent of the gene transcript, and the quantification of gene expression levels, or alternatively, the final gene product itself (protein) can be monitored". Support for the amendment is also found in the specification on page 59, line 2, wherein it is stated that: "BCO2 was up-regulated in breast cancer tissue". Finally, further support for the amendment can be found on page 41, lines 25-28, wherein it is stated that: "The amino acid sequence which is used to determine sequence identity or similarity is that depicted in Figure 2. In another embodiment, the sequences are naturally occurring allelic variants of a protein having the sequence depicted in figure 2". No new matter is added.

Support for the amendments to claims 33 and 35 is found in original claim

1. No new matter is added.

Support for the amendments to claim 38 and newly added claim 39 is found in the specification on page 12, lines 10-14, wherein it is stated that: "A nucleic acid is a 'breast cancer nucleic acid' if the overall homology to the nucleic acid sequences of the figures is... as high as about 93 to 95 or 98%". No new matter is added.

### **The Objections to the Specification**

#### **Priority**

The Examiner objected to the priority claim because neither the first sentence of the specification nor the Application Data Sheet (ADS) contain a specific reference to the prior applications for which the present application is claiming the benefit of priority. The specification has been amended by inserting a paragraph that refers to the priority applications in the first sentence of the specification.

#### **Specification**

The disclosure was objected to because it contained an embedded hyperlink. The specification has now been amended to correct that oversight by eliminating the hyperlink. Those paragraphs that contained the hyperlink were replaced with paragraphs that deleted the hyperlink. No new matter is added.

**Title**

The specification was also objected to because the Examiner alleged that the title was not descriptive of the elected invention. The title has now been amended to refer specifically to methods for detection and diagnosis of breast cancer. Reference to methods of screening for breast cancer modulators has been removed. No new matter is added.

**The Rejections**

**Rejection Under 35 U.S.C. §112 First Paragraph**

*Enablement*

Claims 32-38 are rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in such a way as to enable one skilled in the art to make and use the invention.

The Examiner agrees that the specification is enabling for methods of diagnosis in which increased expression is indicative of the presence of a breast cancer cell. However, the Examiner argues that because SEQ ID NO:1 is not up-regulated in some breast cancer tissue samples, the specification does not enable one to detect the absence of a breast cancer cell.

Furthermore, the Examiner is concerned that the specification does not teach how to use all variants that are at least 80% identical with SEQ ID NO:1. The Examiner alleges that sequences at least 80% identical to SEQ ID NO:1 encompass many thousands of molecules differing from SEQ ID NO:1 in a variety of ways. The Examiner argues that the specification does not disclose that these other molecules are actually found in and/or are up-regulated in breast cancer. Therefore, the Examiner concludes that it is unpredictable as to whether up-regulation of all these possible molecules would be indicative of breast cancer, and therefore states that it would require undue experimentation to practice the methods of the invention with sequences other than SEQ ID NO:1.

To support the rejection, the Examiner cites Billing-Medel. Billing-Medel showed that BS200, which is 99.9% identical to *about half the length* of SEQ ID NO:1, is found predominantly in breast tissue. The Examiner argues that because Billing-Medel do not provide any evidence that BS200 is up-regulated in breast cancer, it is unpredictable whether variants of SEQ ID NO:1 are up-regulated in breast cancer.

It is well established that the Examiner bears the initial burden of providing evidence or reasoning why a pending claim does not meet the requirements of 35 U.S.C. §112, first paragraph. A specification which contains a teaching of the manner and process of making the invention in terms which correspond in scope to those used in claiming the invention must be taken as in compliance with the enablement requirement, unless there is reason to doubt the objective truth of the statements in the specification. To support a rejection under 35 U.S.C. §112, first paragraph, the Examiner must explain why he doubts the truth or accuracy of any statement relied on to establish enablement. The Examiner must also back up assertions of his own with acceptable evidence or reasoning which is inconsistent with the contested statements *In re Marzocchi* 169 USPQ 367 (CCPA 1971) and MPEP 2164.04.

Thus, to support the present rejection, the Examiner must show why one of skill, with knowledge of the correlation between breast cancer and expression levels of BCO2 disclosed here, could not detect breast cancer using the information in the disclosure coupled with techniques well known at the time of the invention.

In an attempt to support the rejection, the Examiner points out that the studies of Billing-Medel fail to provide any evidence about BS200 gene expression in breast cancer. Indeed, the studies merely show that BS200 is found predominantly in breast tissues. To support the Examiner's enablement rejection, Billing-Medel would have to raise doubts that BS200 is up-regulated in individuals who have breast cancer. In the absence of evidence from Billing-Medel that BS200 is *not* up-regulated in individuals who have breast cancer, the Examiner has not provided any evidence to support the a rejection as required by MPEP 2164.04.

To maintain the enablement rejection, the subject matter cited as evidence by the Examiner must support the allegation that one skilled in the art would not be able to make and use the claimed invention commensurate with the scope of the claims. In the absence of evidence that sequences within the scope of the claims are *not* up-regulated in breast cancer, the rejection is improper and should be withdrawn.

*Conclusion*

The Applicants have identified a gene, BCO2, and shown that a high level of expression of the gene is statistically correlated with breast cancer. Thus, determining the expression level of BCO2 is a useful tool for the detection of a breast cancer cell and the diagnosis of breast cancer. Therefore, the disclosure provided by the Applicants is sufficient, when combined with the teachings of the art, to permit one of skill to make and use the invention commensurate with the scope of the claims.

**Rejection Under 35 U.S.C. §112 Second Paragraph**

Claims are also rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter the Applicants regard as their invention. In particular, the Examiner has rejected claims 32-38 over the recitation of the language "detecting a nucleic acid... thereby determining the presence or absence of a breast cancer cell". The Examiner is unclear as to whether the presence of the nucleic acid indicates the presence or absence of a breast cancer cell.

Claim 32 has been amended to recite that "an increase in expression of the nucleic acid in the sample from the patient indicates the presence of a breast cancer cell in the patient". It should now be clear that increased expression of the nucleic acid indicates the presence of a breast cancer cell.

In addition, the defects in all the remaining claims are corrected by this amendment because all the remaining claims are either directly or indirectly dependent on claim 32.

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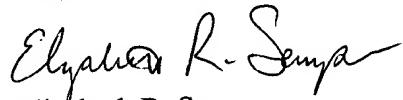
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CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**Changes to the Claims**

32. (Amended) A method for detecting a breast cancer cell [from] in a patient, the method comprising:

(i) detecting a nucleic acid [comprising a] encoding an amino acid sequence at least [80] 90% identical to [SEQ ID NO:1] SEQ ID NO:2 in a sample from the patient, and

(ii) comparing expression levels of the nucleic acid in the sample from the patient to expression levels of the nucleic acid in a normal tissue sample,

[thereby detecting the cancer cell] wherein an increase in expression of the nucleic acid in the sample from the patient indicates the presence of a breast cancer cell in the patient.

33. (Amended) The method of claim 32, wherein the sample from the patient comprises isolated nucleic acids.

35. (Amended) The method of claim 32, wherein the sample from the patient is breast tissue.

38. (Amended) The method of claim 32, wherein said detecting step [further comprises] is carried out by utilizing a biochip comprising a sequence at least 90% identical to SEQ ID NO:1.

39. (New) The method of claim 32, wherein the nucleic acid is at least 95% identical to SEQ ID NO:1.

### **Changes to the Specification**

The substitute paragraph on page 9, lines 9-19 was corrected as follows:

In a preferred embodiment, breast cancer sequences are those that are up-regulated in breast cancer; that is, the expression of these genes is higher in carcinoma as compared to normal breast tissue. "Up-regulation as used herein means at least about a 50% increase, preferably a two-fold change, more preferably at least about a three fold change, with at least about five-fold or higher being preferred. All accession numbers herein are for the GenBank sequence database and the sequences of the accession numbers are hereby expressly incorporated by reference. GenBank is known in the art, see e.g., Benson, DA et al., Nucleic Acids Research 26:1-7 (1998) [and <http://www.ncbi.nlm.nih.gov/>]. In addition, these genes were found to be expressed in a limited amount or not at all in bladder, bone marrow, brain, colon, fibroblasts, heart, kidney, liver, lung, muscle, pancreas, prostate, skin, small intestine, spleen, stomach, and testes.

The substitute paragraph on page 13, lines 4-17 was corrected as follows:

Another example of a useful algorithm is the BLAST algorithm, described in Atschul et al., J. Mol. Biol. 215, 403-410 (1990) and Karlin et al., PNAS USA 90:5873-5877 (1993). A particularly useful BLAST program is the WU-BLAST-2 program which was obtained from Atschul et al., Methods in Enzymology, 266:460-480 (1996) [[<http://wwwblast.wustl.edu/blast/READ.html>]]. WU-BLAST-2 uses several search parameters, most of which are set to the default values. The adjustable parameters are set with the following values: overlap span =1, overlap fraction = 0.125, word threshold (T) = 11. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and the composition of the particular database against which the sequence of interest is being searched; however, the values may be adjusted to increase sensitivity. A % amino acid sequence identity value is determined by the number of matching identical residues divided by the total number of residues of the "longer" sequence in the aligned

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region. The "longer" sequence is the one having the most actual residues in the aligned region (gaps introduced by WU-BLAST-2 to maximize the alignment score are ignored).